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OXYTOCIN INDUCED WATER INTOXICATION

by

Gordon C. Ham

A THESIS

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For the Degree of Doctor of Medicine

Under the Supervision of Robert H. Messer, M.D.

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OXYTOCIN INDUCED WATER INTOXICATION

Introduction

Since the syndrome of water intoxication due to rapid dilution of body fluids by oral and intravenous administration of water was first described by Rowntree in 1923, there have been many reports of cases and experimental studies in the literature. The syndrome usually is iatrogenic and results from administration of large amounts of non-electrolyte solutions, particularly in patients with certain predisposing conditions. These may be conditions in which water excretion is impaired such as cardiac failure, renal insufficiency, and inappropriate ADH (anti-diuretic hormone) secretion from a number of causes including the immediate postoperative state. Conditions in which total body sodium is decreased such as decreased sodium intake, draining fistulas, burns, excessive sweating, prolonged vomiting or diarrhea, use of diuretics, and adrenal insufficiency are also predisposing factors. In addition, water intoxication due to repeated tap water enemas and excessive oral intake have been reported.¹⁸

In 1962, the first report of a case of water intoxication secondary to oxytocin infusion appeared in the literature.⁷ Since then eight similar case reports have been published.^{2, 6, 8, 11, 13, 16, 17, 21}

A recent case in the Department of Obstetrics

and Gynecology at the University of Nebraska Medical Center which represents an example of this phenomenon is presented here.

Case Report

A 24-year-old gravida 3, para 2, married white female who had her last menstrual period May 21-25, 1967, was first seen at the University of Nebraska Hospital and Clinics on September 14, 1967. She had received her prenatal care elsewhere and presented with vaginal bleeding of four days' duration. It was discovered by history that four days previously she had received a shot of an oxytocic intramuscularly and that a plastic catheter had been inserted into her uterus, in an attempt to produce an abortion. The catheter had been removed by the patient just prior to this visit. On the day following insertion of the catheter she developed a temperature of 102° F. and was passing bright red blood per vaginum, using up to 18 pads per day. She started herself on chloromycetin and took 14 capsules over the following two days.

Her past medical history was unremarkable except for abruptio placenta at seven months' gestation in 1965.

At the time of admission the patient was afebrile. The fundal height was 19 cm. and fetal heart tones were present. On pelvic exam, the cervix was noted to be 1 cm. dilated, and active bleeding from the cervix was present.

The cervix and uterus were noted to be quite tender. The remainder of the physical examination was unremarkable. Laboratory studies revealed a hemoglobin of 9.8 gm.% and a white count of 13,100 with a left shift. Urinalysis was negative. A cervical smear was taken for culture.

The patient was admitted with a diagnosis of threatened abortion with possible intrauterine infection. She was started on penicillin, 5 million units in 1000 cc. 5% dextrose in water every six hours, and streptomycin 0.5 gm. intramuscularly every 12 hours. Due to the fact that fetal heart tones were present and the picture had been complicated by self-administered antibiotics, it was decided to watch and wait.

The following day the temperature was normal following elevation to 37.6° C. during the night. The uterus was felt to be more tender with continued vaginal discharge of bloody, watery fluid. It was decided to try to empty the uterus per vaginum with 20 U. oxytocin per 1000 cc. 5% dextrose in water. This was infused at 40-60 drops per minute for approximately 24 hours with no change in the cervix. At this point, it was decided to rest the patient for 24 hours, during which time she received 1000 cc. 5% dextrose in water with 5 million units penicillin and 1 gm. chloromycetin every six hours.

On September 17, 1967, the patient was again started on oxytocin infusion with 60 U. per 1000 cc. 5%

dextrose in water. She received a total of 2750 cc. 5% dextrose in water and 165 U. Syntocinon over 18 3/4 hours, at an infusion rate of 147 mU/minute. At the end of this time a 520 gm. female stillborn was delivered spontaneously.

Immediately post partum the patient became cyanotic and had a grand mal seizure. She had been alert and coherent up until delivery. Her reflexes were 2+, blood pressure 140/70, and no localizing neurological signs were present. At this time a clinical diagnosis of water intoxication was made. She was given 500 mgm. of sodium amytal intravenously and 1000 cc. 20% glucose in water was infused rapidly. A prompt diuresis followed. The patient became comatose and remained in this state for one hour at which time seizure activity recurred and was controlled with 500 mgm. sodium amytal and 100 mgm, phenobarbital. She was then started on lactated ringers with penicillin and chloromycetin, 1000 cc. every six hours.

Blood was drawn for electrolyte determination about one hour after the first seizure, after diuresis had already begun. The following values were obtained, confirming the clinical diagnosis of water intoxication: serum sodium 126 mEq./L; potassium 3.2 mEq./L.; chloride 91 mEq./L.; CO₂ 24 mEq./L.; P.H. 7.4; and serum osmolality 248 mOsm./L.

Following the second seizure, the patient had

bilateral Babinski reflexes and constricted pupils and would convulse with any stimulation. A nasal airway was introduced and oxygen was given. For approximately six hours after delivery she remained comatose and would become cyanotic if the oxygen was stopped. The patient was diuresing well during this time.

The patient's sensorium improved slowly during the next twelve hours. She was able to respond with crying and words and phrases. Electrolytes improved with the diuresis, the serum sodium being 132 mEq./L. and 142 mEq./L. at 7 and 17 hours post partum respectively. The following day the sensorium cleared and the patient was alert and coherent with no memory of the events of the preceding 24 hours. All neurologic signs were normal.

The following two days were uneventful. The patient remained afebrile following a spike to 39.2° C. in the immediately post partum period. She was discharged September 21, 1967, on Ampicillin with no residual effects except amnesia regarding the events following delivery.

Discussion

The pathophysiology of water intoxication is best understood by considering the mechanisms on a cellular level. As the amount of water in the extracellular space increases, there is a simultaneous decrease in the osmol-

arity of the extracellular fluid. This creates an osmotic gradient and water is drawn into nerve cells, thereby giving rise to the cerebral edema of water intoxication. Neuronal function is disturbed and the symptoms appear.¹⁸ These signs and symptoms of water intoxication include nausea and vomiting, headache, somnolence, muscular twitching, tremor, irritability, delirium, convulsions, and finally coma.

Diagnosis of water intoxication depends on the history of water intake, the classical signs and symptoms, and the presence of decreased serum osmolarity. The serum sodium concentration does not effect the nerve cells, but for practical purposes the serum sodium defines the serum osmolarity. Therefore, measurement of the serum sodium is the single most important laboratory test in diagnosis of water intoxication.¹⁸

In most patients with the syndrome of water intoxication, complete reversal of their abnormal neurologic symptoms follows treatment. However, two cases of irreversible brain damage following water intoxication have been reported⁹ as well as one case of acute renal tubular necrosis.¹⁴ One case of a maternal death due to oxytocin induced water intoxication has also been reported.⁸ These potential dangers underscore the importance of prompt diagnosis and treatment.

Because of the close similarity of chemical structure

of oxytocin and the antidiuretic hormone, vasopressin, it may be expected that oxytocin may have some antidiuretic properties. Several investigators have studied the renal effects of oxytocin in man. Some have been unable to demonstrate any antidiuretic action of oxytocin,^{3, 4} but in most of these studies relatively small doses or a negligible water diuresis were employed.¹⁰ On the other hand several more recent studies have shown that oxytocin has a definite antidiuretic action.^{1, 5, 7, 13, 15, 21}

Abdul-Karim and Assali¹ have demonstrated definite antidiuretic activity of oxytocin in pregnant and non-pregnant subjects. When oxytocin is given by continuous infusion, antidiuresis increases with the dose up to 45 mU/minute, but is consistently less than that induced by equivalent doses of vasopressin. Above 45 mU/minute, the antidiuretic effect is comparable in intensity to that of vasopressin, reducing urine flow to less than 10% of pre-infusion levels. However, the duration of the effect of oxytocin is less than that of vasopressin. With oxytocin urine flow returned to control values in 10 to 15 minutes after cessation of infusion whereas flow remained low for 40 to 50 minutes after cessation of vasopressin. It was also demonstrated that the antidiuretic effect of oxytocin was not due to release of endogenous vasopressin by producing similar

results in persons with diabetes insipidus and normal subjects in whom antidiuretic hormone release had been inhibited by alcohol. These results were found to be true for both natural hormone and synthetic oxytocin.

The results of Abdul-Karim and Assali have been confirmed by Whalley and Pritchard.²¹ They obtained an almost identical pattern of dose response to oxytocin with a definite antidiuresis at infusion rates of 10 to 20 mU/minute and greater that 90% reduction in urine flow at rates greater than 50 mU/minute. Infusion rates in excess of 50 mU/minute failed to cause further suppression of urine flow, indicating a maximal antidiuretic response.

Saunders and Munsick¹⁰ have recently studied the antidiuretic effect of commercially available oxytocic preparations in man and also evaluated natural oxytocic preparations for contamination with vasopressin. They found definite antidiuretic response to oxytocin in women post partum. They used single intravenous injections of doses of 100 to 400 mU. In all cases an antidiuretic result was produced. This was contrary to results of other studies using single intravenous injections,¹³ but the doses employed were considerably larger than in the earlier studies. They were also unable to demonstrate any vasopressin contamination of natural oxytocin preparations by pharmacologic studies or column chromatography. This is now of academic concern only, since oxytocin is

now prepared synthetically in pure form.

It may be postulated that renal losses of sodium could contribute to the low serum sodium levels seen in antidiuresis and water intoxication due to oxytocin. It is well known that in the syndrome of inappropriate ADH, urinary excretion of sodium is often increased even though serum sodium is markedly reduced.²⁰ Since the similarity of oxytocin to vasopressin in producing antidiuresis has been demonstrated, it may be concluded that sodium excretion was essentially unchanged during oxytocin infusion except for a decrease in pregnant subjects at term. This decreased sodium excretion in term pregnancy was believed to be due to increased renal dead space in pregnancy.

The previously reported cases of water intoxication due to oxytocin and the case presented here are summarized in Table I. In all but one, convulsions were associated with the hyponatremia following the intravenous infusion of oxytocin. In all cases the dose flow rate of oxytocin was consistent with or greater than that shown to result in maximal antidiuresis by Abdul-Karim and Assali, and Whalley and Pritchard.

In all the reported cases, the oxytocic was given with the non-electrolyte solution, 5% dextrose in water, as the major fluid vehicle. In most cases the amount of electrolyte-free solution was quite large, but this alone should not be sufficient to cause the clinical

syndrome of water intoxication in the normal pregnant individual. Under conditions of water loading, the human kidney is able to excrete dilute urine at up to 20 cc/min. With an additional 1000 to 1500 cc. being eliminated by insensible loss, the water load that can theoretically be handled is phenomenal. Presuming the salt conserving mechanism to be intact, the amount of sodium and other electrolytes lost would be negligible, even in the presence of maximal diuresis.¹² With a normal serum sodium present at the beginning, several hundred mEq. of sodium would have to be lost in a 24 hour period to produce a level low enough to be symptomatic.¹⁷

Although various indications for the use of oxytocin were associated with the cases of water intoxication, it is of interest to note that the induction of labor was in no case the indication for oxytocin. This is generally believed to be because the average dose for induction is 20 mU per minute. However, a recent report describes titration with oxytocin following amniotomy using up to 337 mU. per minute of oxytocin.¹⁹ No cases of water intoxication have occurred, and it has been noted that the oxytocin induced antidiuresis in the normal term pregnancy is temporary and recovery may take place even during continuous infusion.¹⁹

These cases of water intoxication illustrate the importance of restricting the total volume of fluids given

when high doses of oxytocin are used. This may be done by using high concentrations with constant rate infusion pumps. The use of electrolyte-containing solutions may decrease the danger of dilutional hyponatremia but will not prevent water loading and possible circulatory overload.¹⁷

The treatment of water intoxication is basically restriction of further fluids. The excess water will be excreted after the administered oxytocin has been destroyed. However, once the syndrome has progressed to the point of convulsions and coma, it is necessary to institute therapy to decrease cerebral edema rapidly in order to avoid the possibility of serious permanent complications. This is accomplished by increasing the plasma osmolarity by administration of hypertonic solutions. Sodium chloride, glucose, and mannitol have been used successfully. The amount to be given is determined empirically by monitoring the response.

In the treatment of water intoxication, the danger of circulatory overload is an important consideration. For that reason a large volume should not be used in delivering the hypertonic solution. Mannitol, which has been advocated in treating severe cerebral edema,¹⁷ results in a transitory increase in the circulatory volume and may lead to pulmonary edema in situations of pre-existing fluid retention.

Summary

A case of water intoxication in a patient receiving Syntocinon to complete a septic abortion is presented. The pathophysiology, diagnosis, and possible complications of this syndrome are reviewed. The role of oxytocin as an antidiuretic agent and its effect on renal sodium excretion are discussed. The previous cases of water intoxication due to oxytocin are summarized. The role of electrolyte free solutions in development of this syndrome is considered. Oxytocin in the elective induction of labor and potential water intoxication is discussed briefly. The treatment of water intoxication and possible complications thereof is outlined.

TABLE I

CASES OF OXYTOCIN INDUCED WATER INTOXICATION

Author	Year	mU oxy- tocin/min	ml	Fluids Type	Infusion time (hr)	Serum sodium mEq/L.	Convul- sions	Indication	Treatment
Liggins	1962	1366	4500	D ₅ W	10	124	Yes	Missed abortion	D/C oxytocin
Pittman	1963	70	5190 1000	D ₅ W Blood	24	106	Yes	Incompetent cervix and threatened abortion	5% Saline, fluid restriction
Whalley & Pritchard	1963	(1) 150	4000	D ₅ W	8 1/2	114	Yes	Uterine atony	5% Saline
		(2) 333	6500	D ₅ W	35 1/2	115	Yes	Incomplete abortion	5% Saline
Potter	1964	103	3800 1900 1000 690	D ₅ W Normal Saline Blood Oral	42	126	No	Incomplete abortion	Fluid restriction
Silva & Allan	1966	513	5500 500	D ₅ W Oral	26	116	Yes	Incomplete abortion	5% Saline
King & Hall	1966	55	3500	D ₅ W	21	110	Yes	Incomplete abortion	Dextrose in saline, Fluid restriction
Self	1966	166	8000	D ₅ W	18	121	Yes	Incomplete abortion	Mannitol
Brennan, Madden & Massart	1967	133	3000+	D ₅ W	20	120	Yes	Postpartum hemorrhage secondary to retained placental fragments	3% Saline
			1000	Blood					
Lilien	1968	44	4000 450	D ₅ W Blood	23	116	Yes	Incomplete abortion	Mannitol & Normal Saline
Ham	1969	147	2750	D ₅ W	18 3/4	126	Yes	Septic Abortion	20% Glucose in water + Lactated Ringers

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